REMARKS

The Office Action dated December 29, 2003 has been noted, and its contents carefully studied. Reconsideration of the rejection under 35 U.S.C. §§ 102 and 103 is courteously requested.

Claims 1, 3-26, and 28-114 are pending in the present application. Claims 2 and 27 have been cancelled. Claims 1, 3, 26, 28, 59, 63, 64, 72, 87, 92, and 96-105 have been amended as set forth above. Claim 115 has been added to further characterize the invention. The pending claims stand rejected as indicated below. Claims 1, 3-12, 16-17, 20, 23-26, 28-35, 39-40, 43-44, 59-61, 63-72, 74, 76-77, 80, 82, 86, 92-94 and 105-111 are rejected under 35 U.S.C. § 102(a) as being unpatentable over Berner et al. Claims 13, 15, 36, 38, 62, 83, 85, 95-104, 112 and 113 are rejected under 35 U.S.C. §103(a) as being unpatentable over Berner et al in view of Sepaniak et al. Claims 14, 37, 84, and 114 are rejected under 35 U.S.C. §103(a) as being unpatentable over Berner et al in view of Sepaniak et al and further in view of Shehada et al. Claims 19, 21-22, 42, 87-89, and 96-104 are rejected under 35 U.S.C. §103(a) as being unpatentable over Berner et al in view of Eppstein et al. Claims 45-53 and 57 are rejected under 35 U.S.C. §103(a) as being unpatentable over Berner et al in view of Conn et al. Claims 54 and 56 are rejected under 35 U.S.C. §103(a) as being unpatentable over Berner et al in view of Conn et al and further in view of Sepaniak et al. Claim 55 is rejected under 35 U.S.C. §103(a) as being unpatentable over Berner et al in view of Conn et al in view of Sepaniak et al and further in view of Shehada et al. Claim 58 is rejected under 35 U.S.C. §103(a) as being unpatentable over Berner et al in view of Conn et al further in view of Eppstein et al. Claims 73 and 81 are rejected under 35 U.S.C. §103(a) as being unpatentable over Berner et al. Claims 18, 41 and 75 are rejected under 35 U.S.C. §103(a) as being unpatentable over Berner et al in view of Bremer et al. Claims 78-79

are rejected under 35 U.S.C. §103(a) as being unpatentable over Berner et al further in view of Bremer et al and further in view of Ishikawa et al. Claims 90-91 are rejected under 35 U.S.C. §103(a) as being unpatentable over Berner et al further in view of Eppstein et al and further in view of Montecalvo et al.

Rejection of claims 1, 3-12, 16-17, 20, 23-26, 28-35, 39-40, 43-44, 59-61, 63-72, 74, 76-77, 80, 82, 86, 92-94 and 105-111 under 35 U.S.C. § 102(a) as being unpatentable over Berner et al.

Claims 1, 26, 59, 63, 72, 87 92, and 105 have been amended to include the limitation of the sampler being a microfabricated device that utilizes microfluidics. By way of illustration, claim 1 is presented hereunder in its amended form.

1. A transdermal sampling system, comprising:

at least one sampler for retrieving and transferring at least one analyte obtained transdermally from the skin of a subject, wherein the sampler is a microfabricated device comprising a microfluidic assembly;

at least one detector system for identifying and quantifying said at least one analyte; and

at least one logic module for (i) receiving and storing input data from said at least one detector, (ii) relating the input data to other data obtained from the subject relating to the condition of the subject, (iii) displaying output information indicative of health and clinical state of the subject as determined from the relating of the input data to the other data, (iv) transmitting the output information to another system, and (v) controlling the operation of said at least one sampler and at least one detector.

As Berner et al. (hereafter: Berner) do not teach this feature, the undersigned representative respectfully submits that inclusion of this limitation patentably distinguishes the invention of the present application from the reference. Furthermore, it should be noted that this point was also made in the Response to Non-Final Office Action. Specifically, the undersigned representative pointed out that there is no teaching or suggestion in Berner of assembling a microfabricated device with all of the functionality of the claimed device (see page 20 of the Response to Non-

Final Office Action). In the currently pending Final Office Action, the Examiner failed to specifically respond with regards to this point, referring only to Berner's teaching of a "reservoir as sampling unit, a sensing means as the detector system, and a microprocessor means in operative communication with the sampling means and the sensing means as a transmitter/receiver" (see page 14 of the Final Office Action). The undersigned representative therefore respectfully submits that the Examiner failed to fully respond to the representative' earlier arguments and that the finality of the present Office Action is therefore inappropriate. MPEP 706.07 and 707.07(f):

"However, where a single previous Office Action contains a complete statement of a ground of rejection, the final rejection may refer to such a statement and also should include a rebuttal of any arguments raised in the applicant's reply."

"Where an applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it."

The undersigned representative further submits that Berner does not teach a reservoir such as the one of claims 16-17 and 39-40 of the present application. By way of example, claim 16 and 17 recite:

16. (Original) The system of claim 3, wherein said at least one reservoir contains a fluid, and is positioned for transmitting the fluid to a subject's skin to promote flow of said at least one analyte into said at least one conduit.

17. (Original) The system of claim 16, wherein said fluid contained in said at least one reservoir is capable of permeating a subject's skin.

Berner teaches a collection reservoir which is a "containment means for containing a sample extracted from a biological system" which may contain materials such as "a material which is ionically conductive" or "a sponge-like material or a hydrophilic polymer, used to keep the water in place" (col. 6, lines 27-33; emphasis added). That is to say, Berner teaches a reservoir which

is a receptacle for fluid or analyte. The above-referenced claims of the present application claim at least one reservoir which transmits fluid onto the skin of the subject for enhancing analyte uptake by the sampler. Furthermore, Berner does not teach that the reservoir may contain a fluid which is capable of permeating the subject's skin. The undersigned representative therefore respectfully submits that these claims are thus patentably distinct from the teachings of Berner.

In addition, the undersigned representative respectfully submits that the Examiner appears to have made a typing error on page 14 of the Final Office Action, writing "because of the teachings founding column 6, line 60 to column 6, line 50 of Berner et al"; clearly, the first line number should be lower than the second one. For the present response, the undersigned representative has assumed that the Examiner meant to write line 40 to line 50 of column 6 of Berner, and prepared this response in accord with this assumption. If the Examiner intended to write something other than this, he is respectfully urged to note this in the next communication.

Rejection of claims 13, 15, 36, 38, 62, 83, 85, 95-104, 112, 113 under 35 U.S.C. §103(a) as being unpatentable over Berner in view of Sepaniak et al.

According to well-established precedent, the examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. Further, in order to establish a prima facie case of obviousness, three basic criteria must be met:

(1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

(2) there must be a reasonable expectation of success; and

(3) the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Further, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As described above, the independent claims of the pending application have been amended to overcome the rejection over Berner under 35 U.S.C. § 102(a). The undersigned representative respectfully submits that inclusion of the previously-described limitations also overcomes the 35 U.S.C. § 103(a) rejection over of the combination of Berner and Sepaniak et al (hereafter: Sepaniak). As previously noted, Berner does not describe a microfabricated system using microfluidics. Sepaniak teaches that the system described therein can analyze microscale quantities of fluids, but the sampler system as a whole is not microfabricated; e.g., the reagent injection means of Sepaniak, item #50 in their figures, is described as a syringe (at col. 6, lines 3-7), which is clearly not a microfabricated device. The undersigned representative therefore respectfully submits that all the limitations of the present claims are not found in the references (as per requirement #3 above), and requests that this rejection also be withdrawn.

Furthermore, the undersigned representative notes that claims 96-104 have been amended to depend from claim 95, rather than claim 94. Claim 95 reads as follows:

95. The transdermal sampling system according to claim 94, wherein the at least one specific-binding molecule is bound with at least one fluorescently labeled analyte,

wherein the at least one analyte obtained transdermally from the skin of a subject displaces the bound at least one fluorescently labeled analyte, and

wherein measurement of the amount of fluorescence displaced from the at least one specific-binding molecule correlates with the amount of the at least one analyte obtained transdermally from the skin of a subject.

Sepaniak does not teach that the analyte displaces (by competitive binding) a fluorophore from the specific-binding molecule, and that subsequent fluorescence from the displaced fluorophore correlates with the amount of analyte present. Sepaniak only teaches that the product of the reaction between the analyte and a reagent fluoresces (in some instances, by addition of a third component- a separately introduced fluorophore which binds to the reaction product) (see col. 3 lines 44-62 of Sepaniak).

Finally, the undersigned representative notes that claims 95-104 all depend from independent claim 92 (via dependent claim 95), which recites the feature that "at least one surface of the microfluidic assembly is modified in a manner to enhance sampling function" (emphasis added). Sepaniak teaches introduction of a reagent such as antibodies into the reaction (detection) chamber, not the attachment of such reagents to the walls of the sampling system (see, col. 2 lines 32-61). Thus, the modification of the present invention and the modification taught by Sepaniak cannot be equated with the modifications taught in claims 95-104. For the above reasons, the undersigned representative respectfully submits that the Examiner has not fulfilled requirement 3 for establishing a prima facie case of unpatentability, and requests that this rejection be withdrawn.

Rejection of claims 14, 37, 84 and 114 under 35 U.S.C. § 103(a) as being unpatentable over Berner in view of Sepaniak and further in view of Shehada et al.

As described above, the independent claims of the pending application have been amended to overcome the rejection over Berner under 35 U.S.C. § 102(a). The undersigned representative respectfully submits that inclusion of the previously-described limitations also overcomes the 35 U.S.C. § 103(a) rejection over of the combination of Berner, Sepaniak and

Shehada et al (hereafter: Shehada). As argued above, the limitation that the sampler be a microfabricated device utilizing microfluidics is not present in the combination of Berner and Sepaniak; the addition of Shehada to the combination does not remedy this defect. The undersigned representative therefore respectfully submits that these claims, in their present form, are not rendered obvious by the cited references and requests withdrawal of this rejection.

Rejection of claims 19, 21-22, 42, 87-89 and 96-104 under 35 U.S.C. § 103(a) as being unpatentable over Berner further in view of Eppstein

As described above, the independent claims of the pending application have been amended to overcome the rejection over Berner under 35 U.S.C. § 102(a). The undersigned representative respectfully submits that inclusion of the previously-described limitations also overcomes the 35 U.S.C. § 103(a) rejection over of the combination of Berner, and Eppstein et al (hereafter: Eppstein), as the limitation that the sampler be a microfabricated device utilizing microfluidics is not present in either of Berner and Eppstein. The undersigned representative therefore respectfully submits that these claims, in their present form, are not rendered obvious by the cited references and requests withdrawal of this rejection.

In addition, Eppstein teaches the use of sampling techniques such as "needle puncture, hydraulic jet, laser and electroporation". Eppstein also teaches the use of ultrasound energy to "controllably push and/or pump molecules through the stratum corneum via perforations" (see col. 5, lines 15-16). However, the pump of claim 21 does not pump molecules through the stratum corneum, but pumps "fluid into contact with the skin of a subject", wherein the fluid promotes flow of at least one analyte into the conduit for analysis. With regards to the hydraulic

jet sampling taught by Eppstein, it is a technique for skin perforation, not promotion of analyte uptake. Therefore, the pump of claim 21 cannot be equated with the pump action or hydraulic jet sampling described by Eppstein, and, in addition to the previous arguments (regarding Berner), the undersigned representative respectfully requests removal of this rejection.

With regards to the Examiner's assertion that the hydraulic jet sampling taught by Eppstein obviates the pump as claimed in claim 21, the undersigned representative respectfully points out that the present application does not claim hydraulic jet sampling, and further, that Eppstein never defines hydraulic jet sampling. Therefore, even assuming, *arguendo*, that hydraulic jet sampling is taught by Eppstein, the undersigned representative fails to see how this teaches or suggests the claimed limitations and respectfully requests that the Examiner further make clear the relevance of his argument on this point.

The Examiner further asserts that Eppstein teaches a sensor of the analysis of the presence and concentration of an analyte which detects fluorescence. The undersigned representative respectfully submits that the amending of the dependency of claims 96-104 adds features not taught by Eppstein (specifically, the displacement of a fluorophore from a binding molecule by the binding of the analyte), as was previously described in the section regarding the Berner-Sepaniak combination.

Moreover, Eppstein does not teach a fluorescence detection method, but evanescent wave coupling, which is a separate phenomenon and method. Whereas fluorescence involves excitation and subsequent emission of photons (often in separate parts of the electromagnetic spectrum) from a fluorescent molecule, evanescent wave coupling involves the analyte causing attenuation of light energy from the light source to the detector (in Eppstein, both the source and detector are optical fibers); see, e.g., claim 21 of Eppstein. Therefore, fluorescence detection and

evanescent wave coupling cannot be equated. Eppstein teaches the use of lectins for binding glucose, but since Eppstein does not teach fluorescence detection, the undersigned representative respectfully submits that the claimed invention is not rendered obvious by the combination of Berner and Eppstein. Also, Eppstein teaches that the lectins coat the optical fibers, i.e., the detector of the system, whereas in the present invention, the specific-binding molecules are present on the surface of the sampler, not the detector. Finally, the use of lectins to bind the molecule of interest is only the subject of claim 100; the Examiner has failed to point out why he believes that claims 96-99 and 101-104 are rendered obvious by the combination of Eppstein and Berner. The undersigned representative therefore respectfully submits that the combination of Berner and Eppstein does not render these claims obvious and requests that the rejection therefore be removed.

Rejection of claims 45-53 and 57 under 35 U.S.C. § 103(a) as being unpatentable over Berner further in view of Conn et al

As described above, the independent claims of the pending application have been amended to overcome the rejection over Berner under 35 U.S.C. § 102(a). The undersigned representative respectfully submits that inclusion of the previously-described limitations also overcomes the 35 U.S.C. § 103(a) rejection over of the combination of Berner, and Conn et al (hereafter: Conn), as the limitation that the sampler be a microfabricated device utilizing microfluidics is not present in either of Berner and Conn. The undersigned representative therefore respectfully submits that these claims, in their present form, are not rendered obvious by the cited references and requests withdrawal of this rejection.

Furthermore, the undersigned representative notes that claim 57 recites as follows:

57. The device of claim 46, wherein said silicon body comprises at least one reservoir capable of containing a fluid, and in communication with said capillary conduits, for transmitting the fluid to a subject's skin to promote flow of said at least one analyte into at least one of said capillary conduits.

As previously noted (with regards to claims 16-17), Berner does not teach a reservoir for transmitting a fluid onto the subject's skin to promote analyte uptake. The undersigned representative respectfully submits that the addition of the teachings of Conn does not cure this deficiency and therefore requests removal of this rejection.

Rejection of claims 54 and 56 under 35 U.S.C. § 103(a) as being unpatentable over Berner in view of Conn and further in view of Sepaniak

As described above, the independent claims of the pending application have been amended to overcome the rejection over Berner under 35 U.S.C. § 102(a). The undersigned representative respectfully submits that inclusion of the previously-described limitations also overcomes the 35 U.S.C. § 103(a) rejection over of the combination of Berner, Conn and Sepaniak, as the limitation that the sampler be a microfabricated device utilizing microfluidics is not present in either of the three references. The undersigned representative therefore respectfully submits that these claims, in their present form, are not rendered obvious by the cited references and requests withdrawal of this rejection.

Rejection of claim 55 under 35 U.S.C. § 103(a) as being unpatentable over Berner in view of Conn in view of Sepaniak and further in view of Shehada

As described above, the independent claims of the pending application have been amended to overcome the rejection over Berner under 35 U.S.C. § 102(a). The undersigned

representative respectfully submits that inclusion of the previously-described limitations also overcomes the 35 U.S.C. § 103(a) rejection over of the combination of Berner, Conn, Sepaniak, and Shehada, as the limitation that the sampler be a microfabricated device utilizing microfluidics is not present in either of the three references. The undersigned representative therefore respectfully submits that these claims, in their present form, are not rendered obvious by the cited references and requests withdrawal of this rejection.

Rejection of claim 58 under 35 U.S.C. § 103(a) as being unpatentable over Berner in view of Conn further in view of Eppstein

Claim 58 is presented as follows:

58. The device of claim 57, wherein said silicon body further comprises a microheater disposed to be in close proximity to a subject's skin surface at a location proximate to where said fluid is pumped into contact with the skin of a subject, and is configured for ablating a portion of the stratum corneum of the skin of a subject.

As described above, the independent claims of the pending application have been amended to overcome the rejection over Berner under 35 U.S.C. § 102(a). The undersigned representative respectfully submits that inclusion of the previously-described limitations also overcomes the 35 U.S.C. § 103(a) rejection over of the combination of Berner and Eppstein, as the limitation that the sampler be a microfabricated device utilizing microfluidics is not present in either of the references. The undersigned representative therefore respectfully submits that these claims, in their present form, are not rendered obvious by the cited references and requests withdrawal of this rejection.

Moreover, the Examiner admits (on page 9 of the present Office Action), that "the combination does not teach the use of a pump for pumping the fluid which promotes the flow of the analyte to the sampler", but then goes on to argue that it would have been obvious, in view of

the combination, to substitute a hydraulic jet sampling method for electroporation, laser sampling, or needle punctures. It should first be noted that the pending application does not claim hydraulic jet sampling. Furthermore, hydraulic jet sampling is a technique for perforating the skin, not for the pumping of fluid to promote the flow of analyte to the sampler. Finally, even if one assumes, *arguendo*, that hydraulic jet sampling is taught by the combination of references, the Examiner has (by his own admission) failed to point out how the limitations of claim 58 are taught by the combination of references. The undersigned representative therefore respectfully requests that this rejection be withdrawn.

Rejection of claims 73 and 81 under 35 U.S.C. § 103(a) as being unpatentable over Berner

As described above, the independent claims of the pending application have been amended to overcome the rejection over Berner under 35 U.S.C. § 102(a), by including the limitation that the sampler be a microfabricated device utilizing microfluidics . The undersigned representative respectfully submits that inclusion of this limitation also overcomes the 35 U.S.C. § 103(a) rejection over Berner, as the limitation is not taught by the reference. The undersigned representative therefore respectfully submits that these claims, in their present form, are not rendered obvious by the cited reference and requests withdrawal of this rejection.

Rejection of claims 18, 41, and 75 under 35 U.S.C. § 103(a) as being unpatentable over Berner further in view of Bremer et al

These claims are directed to the limitation of a breakable seal. By way of example, claim 18 is presented as follows:

18. The system of claim 16, further comprising a breakable seal for retaining said fluid in said reservoir prior to sampling analytes from a subject.

Claim 115 has been added in the current application to further characterize the seal (as being semi- and selectively permeable).

As described above, the independent claims of the pending application have been amended to overcome the rejection over Berner under 35 U.S.C. § 102(a) by including the limitation that the sampler be a microfabricated device utilizing microfluidics. The undersigned representative respectfully submits that inclusion of this previously-described limitation also overcomes the 35 U.S.C. § 103(a) rejection over of the combination of Berner and Bremer et al. (hereafter: Bremer), as the limitation is not present in either of the references. The undersigned representative therefore respectfully submits that these claims, in their present form, are not rendered obvious by the cited references and requests withdrawal of this rejection.

Furthermore, (as previously argued with regards to claims 16-17) it should initially be noted that Berner only teaches a collection reservoir, not a reservoir for containing a fluid for promoting flow of an analyte into a conduit for analysis, and that the teachings of Bremer do not cure this defect. Even assuming, *arguendo*, that the claimed device and the combined references are analogous even with this distinction, the seal described by Bremer et al. is a "peelable, non-permeable strip sheet or film" (see col. 6, lines 13-15 and item #90 in Bremer's figures). Thus, it is clearly distinct from the breakable seal of the present application, as Bremer's seal must be "peeled" or "stripped" prior to use of the device (see, col. 6 lines 13-21), and is not therefore intended to be breakable during the course of normal operation of the device; i.e., it is a removable seal, not a breakable one. The undersigned representative respectfully submits that this point was also made in the Response to Non-Final Office Action (see page 23 of the Response to Non-Final Office Action), and that the Examiner has failed to provide a response to this argument (focusing only on the issue of the seal being semi- and selectively permeable).

The undersigned representative therefore respectfully submits that the Examiner failed to fully respond to the representative' earlier arguments; the finality of the present Office Action is therefore inappropriate and the undersigned representative hereby requests that the final rejection be withdrawn as premature (see MPEP 706.07 and 707.07(f)). The undersigned representative therefore respectfully submits that the combination of Berner and Bremer does not render these claims obvious and requests that the rejection be removed.

Rejection of claims 78 and 79 under 35 U.S.C. § 103(a) as being unpatentable over Berner further in view of Bremer and further in view of Ishikawa

Claims 78 and 79 are presented as follows:

78. The transdermal sampling system according to claim 76, wherein the micro-heating element serves to rupture the at least one seal.

79. The transdermal sampling system according to claim 76, wherein the micro-heating element serves both to ablate stratum corneum and to rupture the at least one seal.

As described above, the independent claims of the pending application have been amended to overcome the rejection over Berner under 35 U.S.C. § 102(a) by including the limitation that the sampler be a microfabricated device utilizing microfluidics. The undersigned representative respectfully submits that inclusion of this previously-described limitation also overcomes the 35 U.S.C. § 103(a) rejection over of the combination of Berner, Bremer, and Ishikawa et al. (hereafter: Ishikawa), as the limitation is not present in either of the references. The undersigned representative therefore respectfully submits that these claims, in their present form, are not rendered obvious by the cited references and requests withdrawal of this rejection.

Though Ishikawa teaches the use of a heater to rupture a seal (though, notably, in the context of an implantable drug delivery system, not in the context of a device for transdermal monitoring of analytes), that does not overcome the inadequacy that Bremer does not teach a

breakable seal for a transdermal device, nor the Examiner's failure to fully respond to the undersigned representative arguments in the Response to Non-Final Office Action (as argued above). The undersigned representative therefore respectfully submits that the limitations of these claims are not found in the references and requests removal of this rejection.

Rejection of claims 90 and 91 as being unpatentable under 35 U.S.C. § 103(a) over Berner further in view of Eppstein and further in view of Montecalvo et al

As described above, the independent claims of the pending application have been amended to overcome the rejection over Berner under 35 U.S.C. § 102(a) by including the limitation that the sampler be a microfabricated device utilizing microfluidics. The undersigned representative respectfully submits that inclusion of this previously-described limitation also overcomes the 35 U.S.C. § 103(a) rejection over of the combination of Berner and Montecalvo et al. (hereafter: Montecalvo), as the limitation is not present in either of the references. The undersigned representative therefore respectfully submits that these claims, in their present form, are not rendered obvious by the cited references and requests withdrawal of this rejection.

CONCLUSION

The undersigned representatives reserve the right to file continuations to seek protection for other novel aspects of the present invention, including those included in any cancelled claims.

For all of the above reasons, it is respectfully submitted that the claims now pending patentably distinguish the present invention from the prior art of record. Accordingly, reconsideration and withdrawal of the outstanding prior art rejections and an issuance of a Notice of Allowance are earnestly solicited. Should the Examiner have any comments, questions or suggestions of a nature necessary to expedite prosecution of the application, he/she is courteously requested to contact the undersigned representative at the number listed below.

Respectfully submitted,

Date: 3/10/04

By: _____ (Reg. no. 52,856)
for Dawn-Marie Bey
Registration No. 44,442

KILPATRICK STOCKTON LLP
Suite 900
607 14th Street, N.W.
Washington, D.C. 20005
(202) 508-5800 (phone)
(202) 508-5858 (fax)